REMARKS

Applicant respectfully requests reconsideration. Claims 1-3, 6-26, and 29 were previously pending in this application. By this amendment, Applicant is canceling claims 1, 6-24, and 29 without prejudice or disclaimer, as being drawn to a non-elected invention. Claims 2 and 3 have been amended. Support for the amendment can be found in the specification as filed at least at page 2, lines 28-31. New claims 30-33 have been added. Support for the new claims 30-33 can be found in the specification as filed at least at page 2, lines 28-31. As a result, claims 2, 3, 25, 26, and 30-33 are pending for examination with claims 2 and 3 being independent claims. No new matter has been added.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 2, 3, 25 and 26 under 35 U.S.C. §103(a) as being unpatentable over Neale et al. (Meeting abstract Am J. Obs & Gyn 2001;185(6s-1) page S83, 22nd Annual Meeting of the Society for Maternal-Fetal Medicine).

To support a *prima facie* case for obviousness, the Examiner must demonstrate motivation to combine the teachings in the references to make the claimed invention, a reasonable likelihood of success in making the combination of references, and that the references teach every element of the claimed invention. Applicant has amended claims 2 and 3 to clarify that the serum or plasma is obtained from the pregnant woman as early as the first trimester of pregnancy. With respect to the claims as amended, the requirements for a *prima facie* case of obviousness have not been met.

The Examiner appears to have erroneously attributed features of the claimed invention to the Neale et al. abstract. The Examiner states at page 2 of the Office Action mailed July 20, 2007 that Neale et al.:

> ...teach a method for predicting of (*sic*) preeclampsia, comprising (a) culturing human trophoblast cells in the presence of (i) anti-Fas antibodies (line 4) and (ii) serum or plasma obtained from a pregnant woman to be assessed for risk of developing preeclampsia (line 4); (b) culturing an equivalent sample of human trophoblast cells under the same condition as cells in (a) but in the absence of serum or plasma obtained from a pregnant woman to be assessed for risk of developing preeclampsia (control in line 4); and (c) comparing viability of cells

> cultured in (a) with the viability of cells cultured in (b), wherein if fewer cells cultured in (a) than cells cultured in (b) are viable, the woman is determined to be at risk of developing preeclampsia (lines 8-9); (d) culturing an equivalent sample of human trophoblast cells under the same conditions as cells in (a) but in the presence of serum or plasma obtained from a normal control (control in line 4); and (e) comprising viability of cells culture in (a) with the viability of cells cultured in (d), wherein if fewer cells cultured in (a) than cells cultured in (d) are viable, the woman is a risk of developing preeclampsia (lines 14-16)

Applicant submits that although this quoted paragraph describes the claimed invention, contrary to the Examiner's stated conclusion, the Neale et al. abstract does not teach or describe these methods. The Examiner appears to have mistakenly attributed the disclosure of the above-quoted methods to the Neale et al abstract. Subsequently, at page 3 of the Office Action, the Examiner does indicate that Neale et al. does not teach a method of determining if a pregnant women is at risk of developing preeclampsia.

The Neale et al. abstract describes identification of a component that is present in serum or blood of a woman with preeclampsia and reduces trophoblast viability. Such a disclosure does not render the invention obvious. The claimed assay does not simply identify the presence of a component that alters trophoblast viability or confirm the presence of preeclampsia in a woman but can be used as early as the first trimester of pregnancy to predict risk of later onset of preeclampsia in a woman who does not have preeclampsia. The prediction of risk of later onset of preeclampsia is very different from the identification of a serum component as was described in the Neale et al. abstract. The identification by Neale et al. that a component of serum is associated with existing preeclampsia would not have lead one of ordinary skill in the art to predict that the component could be assayed as early as the first trimester of pregnancy to predict that a woman is at risk of developing preeclampsia later in pregnancy.

The identification of components in blood or serum of patients with disease has been undertaken for many years. For example, at the time of filing, there were numerous serum components known to be present in women with preeclampsia. Although some of the components would have been indicators of the presence of preeclampsia, many others were simply present and were not diagnostically useful. Although the Neale et al. abstract identifies that a component that reduces trophoblast viability is present in serum or blood of women with preeclampsia, there is no

teaching that it is *diagnostic* for preeclampsia. The presence of a component in blood or serum of a patient with a disease frequently is not diagnostic of a disease. For example, at the time of filing, compounds such as IL-10, IL-4, activin A, HGC, progesterone, and estrogen, among others, had been identified as being present in serum of preeclamptic patients, but these components are not diagnostic for preeclampsia and certainly cannot be used as early as the first trimester of pregnancy to assess risk of future development of preeclampsia in a pregnant woman. Thus, at the time of filing, one of ordinary skill in the art would have had no reasonable expectation of success in taking an assay for a component simply identified as being present in women with existing preeclampsia and modifying that assay to identify risk of developing preeclampsia in a woman as early as the first trimester of pregnancy.

A second factor that supports a conclusion of non-obviousness of the claimed invention lies in the level of knowledge in the art at the time of filing. The understanding of diagnostics and preeclampsia at the time of filing was such that one of ordinary skill would not have been motivated to use the claimed assay method of Neale et al. to test non-preeclamptic pregnant women as early as the first trimester of pregnancy to predict whether or not the women would later develop preeclampsia. Even if, *in arguendo*, one had been motivated to modify the assay of Neale et al. for use in early stage pregnancy, the art-held beliefs regarding diagnostics and the clinical progression of preeclampsia support a conclusion that there would have been no reasonable expectation of success in making the claimed invention based on the teaching of the Neale et al. abstract.

Submitted herewith is a Declaration of Dr Gil Mor that provides evidence of (1) the unexpected nature of the assay for the prediction of the later development of preeclampsia and (2) the state of knowledge regarding diagnostics and preeclampsia held in the art at the time of filing. As indicated in the Declaration, at the time of filing, the relevant scientific community was did not accept that Dr. Mor's assay could detect risk of preeclampsia in pregnant women in the early stages of pregnancy. Editors of a number prominent scientific journals provided negative feedback to Dr. Mor regarding use of his assay as an early predictor of preeclampsia and his work remained unpublished. As indicated in the Dr. Mor's Declaration, editors of journals such as *Human Reproduction*, *Journal of Immunology*, and *Journal of Obstetrics and Gynecology* expressed disbelief that preeclampsia would initiate detectable changes several months in advance of the onset

of clinical symptoms. The understanding held by such skilled artisans was that preeclampsia had an acute onset and that risk of preeclampsia was not an identifiable phenomena at such an early time in pregnancy. Thus, Dr. Mor's identification that the risk of developing preeclampsia could be predicted months in advance of the onset of preeclamptic clinical symptoms was not accepted by those knowledgeable in the art at the time of filing. Both the state of understanding in the art at the time of filing, and the unexpected nature of the assay to work in very early pregnancy support a conclusion that the claimed invention was not obvious at the time of filing. It would not have been predictable to take the assay of Neale et al., and modify it to make an assay to be used as early as the first trimester of a pregnancy to predict the later development of preeclampsia. Thus, Applicant respectfully submits that the claimed invention was not obvious at the time of filing.

There is no teaching in Neale et al. that a trophoblast assay would be useful as a predictor of future onset of preeclampsia. The state of understanding of diagnostics and preeclampsia in the art at the time of filing argue strongly in favor of a finding of nonobviousness of the invention as claimed. Those of skill in the art at the time of filing held the view that such early detection methods would not be possible in a disorder such as preeclampsia, which was believed not to include detectable changes several months in advance of the onset of clinical symptoms. Thus, the Examiner's conclusion at page 3 of the Office Action that one of ordinary skill in the art at the time of filing would have been motivated to modify the teaching of Neale et al, to make the claimed invention, and that such a person would have a reasonable expectation of success is not supported by the state of the art or understanding held by those of ordinary skill in the art at the time of filing. It is only through improper use of hindsight that a conclusion of obviousness can be reached. Applicant submits that a *prima facie* case for obviousness has not been made.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 2, 3, 25, and 26 as unpatentable over Neale et al.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: December 20, 2007

Respectfully submitted,

By _____

MaryDilys S. Anderson, Ph.D.
Registration No.: 52,560
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
(617) 646-8000